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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,733	10/01/2003	Kevin H. Gardner	UTSD:1510	4887

23379 7590 09/05/2006

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,733	GARDNER ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The application has been amended as requested in the communication filed June 21, 2006. Accordingly, claims 1 and 2 have been amended.

The terminal disclaimer filed on June 21, 2006 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of U. S. patent 6,319,679 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The examiner acknowledges receiving the declaration of Professor Stephen S. Sprang filed under 37 CFR 1.132. Contrary to item 1 of the declaration, it contains no *curriculum vitae*.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "foreign ligand" in claim renders the claim indefinite because the resulting claim does not set forth the metes and bound of the claimed invention for the reasons set forth in the prior Office action mailed 2/21/06.

In response the above, applicants argue that the phrase is defined in the specification.

Applicants' arguments and the declaration of Stephen R. Sprang filed 6/21/06 have been fully considered, but they are found unpersuasive. A ligand is a ligand. A ligand is a chemical compound having any structure that is capable of binding to PAS domain. The specification does not describe how to differentiate between a "foreign ligand" or a "non-foreign lignad".

(b) The clause "that has no NMR-apparent a priori formed ligand cavity" in claim 1 renders the claim indefinite and confusing for the reasons set forth in the prior Office action mailed 2/21/06.

In response the above, applicants argue that the clause is self-explanatory and one of ordinary skill in the art would know its meaning.

Applicants' arguments and the declaration of Stephen R. Sprang filed 6/21/06 have been fully considered, but they are found unpersuasive. The specification failed to characterize the active site residues and their NMR

chemical shifts involved in binding the ligand. In real life experiment, the ordinary skill in the art would be expected to record NMR spectra in the presence and absence of a ligand. If, in the presence of a ligand, the NMR signals of the protein and/or the ligand have sharpend, brodened, or change their chemical shifts, the ligand must be bound specifically to the protein. It is well established that some NMR signals may not be observed for the non-ligated protein due to the fact that the active site residues are changing their conformation slowly on the NMR time scale or large mobility in a portion(s) of the protein, but the binding-site is fully formed and functional and the protein is capable of carrying out its function.

(d) The phrase "to infer the presence of the ligand specifically bound" in claim 1 renders the claim indefinite because the resulting claim does not set forth the metes and bound of the claimed invention for the reasons set forth in the prior Office action mailed 2/21/06.

In response the above, applicants argue that the clause is self-explanatory and one of ordinary skill in the art would know its meaning.

Applicants' arguments and the declaration of Stephen R. Sprang filed 6/21/06 have been fully considered, but they are found unpersuasive. The mere comparison of two NMR spectra by itself is not sufficient to infer specificity of a bound ligand. It is the observation of changes in the chemical shifts and ordered structure in otherwise disordered region that infer the specificity of the ligand.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fesik *et al.* (WO 97/18471) in view of any one of U. S. patents 5,843,683 ('683, Edery *et al.*); 6,291,429 ('429, Takahaski *et al.*); 6,436,654 ('654, Berkenstam *et al.*) for the reasons set forth in the prior Office action mailed 2/21/06.

In response the above, applicants argue that structurally characterized PAS domains without a bound cofactor show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligands.

Applicants' arguments and the declaration of Stephen R. Sprang filed 6/21/06 have been fully considered, but they are found unpersuasive. The claims are not limited to a method of identifying a molecule that bind to a pass domain in a specific binding cavity in a PAS domain. The PAS domains are known to have specific biological function through interaction with other proteins and other molecules. The '683 patent teach a method to identifying, screening, and characterizing compounds potentially useful for treatment of diseases or disorder arising abnormal PAS-PAS binding affinities by contacting the PAS protein or domain with potential compound. See column 3, lines 32-45. This is essentially the same claimed method except that the method of the instant claims requires the detection by NMR methods. Thus, the teaching of '683 motivates one of ordinary skill in the art to develop a method to identify compounds that bind to PAS domain. Fesik *et al.* have tabbed the NMR technology to identify compounds that bind proteins. Thus, the ordinary skill in the art would have had the motivation, the teaching of the art, and the skill to develop the claimed method and use it to identify compound that bind to a PAS domain. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

In addition to the above, whatever the meaning of the clause "has no NMR-apparent a priori formed ligand cavity", it does not distinguish between the claim and the prior art. The fact the NMR method can't observe certain signals in the absence of a ligand, does not mean that the ligand-binding site is not formed or incompetent. The major advantage of NMR techniques over the X-ray method is that it observes a protein molecule in its native environment, i.e., in aquious solution. Unlike crystals, protein molecules are neither static nor stationary in solution. Various portions of the molecule are constantly sampling different conformations and orientation relative to the magnetic field, i.e., tumbling in the magnetic field. If the changes are fast on the NMR experiment time scale, an average signal will appear for all the conformer and position of the molecule relative to the magnetic field. If, however, the conformation changes are slow relative to the time scale, the NMR signals of some residues become broader or not observable at all in many cases. With regard to binding to the hydrophobic core, all folded proteins have hydrophobic core, and many can bind "foreign ligand" specifically in a cavity in the protein unrelated to its function. The binding has to occur in a hydrophobic environment otherwise the binding would not take place all together.

No claim is allowed.

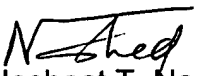
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656